REMARKS

This Reply is responsive to the Office Action dated May 4, 2001. Entry of the foregoing and reconsideration on the merits pursuant to 37 CFR 1.112 is respectfully requested.

First, the specification has been amended to include cross reference to related applications, and to define the various sections of the application as requested on pages 2-3 of the Office Action. A new abstract was also submitted to replace the prior abstract, which takes into account the recommendations set forth in the Office Action on page 2. No new matter was added.

In addition, claims 1-12 were canceled and new claims 14-22 were submitted. Support for the new claims may be found in the original claims, which are part of the original disclosure. For instance, new claim 14 is essentially the same as original claim 1 into which the features of original claim 6 have been incorporated. Similarly, new claim 15 is essentially the same as original claim 2 into which the features of original claim 5 have been incorporated. No new matter has been added.

Turning now to the Office Action, claims 6-7, 9 and 11 were objected to under 37 CFR 1.75(c) as being in improper form because a multiply dependent claim cannot be dependent on any other multiply dependent claim. The objected claims have been replaced by new claims 14-22, in which no multiply dependent claim depends from any other multiply dependent claim. Therefore, the objection should not be applicable to the newly submitted claims.

Appropriate correction of the specification was required to incorporate appropriate section headings and replace the phrase "The figures show . . ." with the phrase "Brief Description of the Drawings." The requested amendments have been made as submitted above.

Claims 1-12 were rejected under 35 U.S.C. §112, second paragraph for alleged indefiniteness due to use of the word "characterized." Claims 1-12 have been replaced by new claims 14-22, which use the more common term "wherein" instead of the phrase "characterized in that." No new matter has been added because "wherein" and "characterized in that" have the same meaning. Thus, the rejection under 35 U.S.C. §112, second paragraph should not be applicable to newly submitted claims 14-22.

Claims 1-12 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over the combination of Bergmann et al. (USP 5,814,461) and/or Morris et al. (J. Biol. Chem, May 1993) in view of Morgenthaler et al. (J. Clin. Endocrinol. Metab., Feb. 1996). Essentially, the Examiner's position is that, although Bergmann differs from the present invention by immobilizing labeled TSH specific antibody instead of immobilizing the recombinant human TSH receptor, and differs in that the bovine TSH receptor is used rather than the recombinant human receptor, and differs in that labeled TSH specific antibody was used as a tracer instead of labeled bovine TSH, such differences are allegedly inconsequential in view of the disclosures of Morris and Morgenthaler. Specifically, the Examiner believes that it would have been obvious at the time the invention was made to substitute the recombinant human TSH receptor as taught by Morgenthaler or Morris and the bovine TSH as taught by Morris in the methods of Bergmann to arrive at the present invention. Motivation to make the substitution is allegedly found in the teaching in Morris et al of the specific residues of human TSH receptor involved in hormone binding, and in the teaching in Bergmann that human anti-TSH receptor autoantibodies in Graves' disease would bind to the human recombinant receptor with improved specificity and sensitivity over assays that utilize porcine receptor. Applicants respectfully traverse the rejection.

The present invention concerns assays for the determination of pathological autoantibodies against the TSH receptor which play a role in a number of thyroid disorders, the most prominent of which being Graves' disease. The assay which dominated the art for years, as described in the introductory portion of the specification, was an assay which relied on the competitive binding of the population of the autoantibodies being measured and labeled bovine TSH (bTSH) to a solubilized porcine TSH receptor, followed by a final precipitation step. For years our clients worked to develop a "solid-phase" assay which did not require the precipitation step but in which - as is conventional in many assays for the determination of other biological molecules - at the end of the assay the resulting proportional amount of bound label is found bound to a solid phase, e.g. a coated tube, which, after separation from the liquid reaction mixture, can be directly introduced into the measurement procedure or device. However, due to the delicate properties of the TSH receptor molecule (TSHR) used as specific binder, a solid phase assay that could compete with the previously existing precipitation assay or that was of a better quality than the previous precipitation assays was difficult to produce.

The assay claimed in the present application is the assay that finally replaced the traditional "precipitation assay" to which it gives clearly superiour results. The characteristic features of the new "second-generation" assay include the use of a functional recombinant human TSH receptor (as recited in claims 14 and 15), which is immobilized by means of a special type of monoclonal antibody which preferably recognizes only conformational epitopes of the human TSH receptor and which can be obtained by immunization with a TSHR DNA construct (see new claim 17).

The use of a human TSH receptor gives more relevant results than the previous assays using a solubilized porcine TSHR, but also creates some additional considerations. Human TSH (i.e. the hormone itself), which is present in some sera of patients, did not react with the conventional porcine TSH receptor but is reactive with the human TSH receptor. In order to "neutralize" human TSH, an antibody against human TSH is preferably added to the assay (new claim 20). Further, many sera contain constituents which bind to the bovine labeled TSH (bTSH) used as tracer and, therefore, interfere with the tracer binding to a human TSH receptor. By carrying out the assay as two-step assay (claim 14), the tracer is added in a second step when patient sera are not present anymore, thereby improving assay quality even further.

The rejection under 35 U.S.C. §103(a) is based in part on Bergmann, which is U.S. patent 5,814,461. The Examiner is essentially correct in summarizing the teachings of Bergmann, and also correct to note that the present invention is clearly distinguished by using an immobilized recombinant human TSH receptor. In Bergmann, an antibody to bTSH is immobilized. Bergmann reflects the earlier attempts to create some sort of a solid phase assay in former times when attempts to immobilize a TSH receptor did not give satisfactory results. At the time of Bergmann, immobilized TSH receptor preparations were not functional, and the binding of the tracer (labeled TSH) and/or the autoantibodies to be determined to such immobilized TSH receptor was impaired such that no useful, competitive solid phase assay using an immobilized TSHR could be designed.

Morris would not have made up for the deficiencies of Bergmann so as to render the present invention obvious. Morris deals with the determination of TSH (i.e. the hormone) binding epitopes of the hTSHR using crude thyroid membranes containing receptors in native, membrane bound form in a conventional precipitation assay. Morris is silent with respect to the use of a functional hTSHR immobilized to a solid support. Further, Morris

does not address the binding of autoantibodies to the TSH receptor. Thus, Morris neither discloses nor suggests a method as claimed in claims 14 and 15 of the present application. Given the difficulties that the skilled artisan faced at the time of Bergmann in immobilizing a functional TSH receptor to a solid support for the determination of autoantibodies, Morris discloses nothing that makes up for the absence of this teaching in Bergmann.

Morgenthaler, discussed on page 11, lines 5 to 22 of the present application, is a paper which describes the competition of pathological autoantibodies for certain epitopes of the human TSH receptor, using an immunoprecipitation technique employing an ^{35}S-labeled TSHR. Using this technique Morgenthaler carried out epitope mapping of the hTSHR for "some" autoantibodies. It was found that about 70% of the autoantibodies present in the sample tested bound to the extracellular domain of the hTSHR (TSH-R.E) used.

Morgenthaler does not address the problem as to how a functional immobilized hTSHR could be prepared, and neither describes nor suggests an assay as claimed in (new) claim 14 or claim 15. The immunoprecipitation technique for a limited sample of antibodies as described in Morgenthaler does not suggest using the hTSHR as a binder for a solid phase assay that aims to detect all the pathological autoantibodies to the hTSHR in a given sample. Moreover, the use of a ^{35}S-labeled receptor as employed in Morgenthaler is unsuitable for clinical routine.

Thus, it would not have been obvious to one of skill in the art at the time the present invention was made to use an immobilized human TSH receptor in assays for detecting autoantibodies to TSH receptor based on the cited references. Bergmann is clearly lacking in such a teaching as acknowledged by the Examiner, and neither Morris nor Morgenthaler teach a method for immobilizing a human recombinant TSH receptor to a solid support for use in such an assay. The difficulty experienced by those in the art in immobilizing a functional receptor to a solid support suggests that the mere knowledge of the receptor alone is not enough to render the invention obvious. Reconsideration and withdrawal of the rejection under §103(a) based on Bergmann, Morris and Morgenthaler is therefore respectively requested.

All issues raised by the Office Action dated May 4, 2001, have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. If the Examiner has any further

questions or issues to raise regarding the subject application, it is respectfully requested that she contact the undersigned so that such issues may be addressed expeditiously.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: _____
Bonnie D. Weiss
Registration No. 43,255

1600 Tysons Boulevard
McLean, VA 22102
(703) 905-2000 Telephone
(703) 905-2500 Facsimile

Attorney Reference: 011377-0263260

Date: November 2, 2001